REMARKS

Claims 1-3, 5-7, 9-11, 13, 15-17, 25, 26, and 28-32 are pending in the application. Claims 10, 25, 26, 28-30, and 32 are withdrawn as being drawn to non-elected inventions. Claims 1-3, 5-7, 9, 11, 13, 15-17, and 31 are under active consideration.

Claims 1, 11, and 16 have been amended. To expedite prosecution, claim 1 has been amended to recite that the claimed variants and fragments stimulate DnaK ATPase activity, and claim 11 has been amended to recite that the claimed polynucleotide variants encode a polypeptide that stimulates DnaK ATPase activity. Support for the amendment of claims 1 and 11 can be found in the specification, for example, at Table 2, which identifies the DnaJ homolog hlj1p (g972936) as a homolog of the SEQ ID NO:11 polypeptide and points out the presence of DnaJ motifs in SEQ ID NO:11, and at page 68, which describe an assays for measuring the activation of HSP70 ATPase activity by HCPN. In addition, a recent BLAST analysis (Exhibit A) shows that SEQ ID NO:11 is homologous to other J-domain containing proteins. By this amendment, Applicants expressly do not disclaim equivalents of the invention which could include polypeptides having biological activities in addition to the recited DnaK ATPase stimulatory activity or polynucleotides encoding such polypeptides. These amendments further clarify the intended subject matter of the claimed invention and address the rejections under 35 U.S.C. § 112, first paragraph. Claim 16 has been amended to address the rejection under 35 U.S.C. § 112, second paragraph. These amendments further clarify the intended subject matter of the claimed invention. Entry of these amendments is respectfully requested.

Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

Comments Regarding Restriction Requirement

Applicants affirm the election with traverse of Group 21, which corresponds to claims 3, 5-7, 9, and 11 drawn to polynucleotides. Applicants thank the Examiner for rejoining claims 1, 2, 13, 15-17, and 31 with the claims of Group 21.

Rejoinder

Applicants reiterate their request that claims 28 (Group 86) and 32, drawn to methods of using the polynucleotides, be rejoined, and in addition, request that claims 25 and 26, drawn to

methods of using the polypeptides, be rejoined per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Applicants request that claims 28 (Group 86) and 32 be rejoined and examined upon allowance of any of the claims drawn to the polynucleotides of Group 21 and that claims 25 and 26 be rejoined and examined upon allowance of any of the claims drawn to the polypeptides.

Objection to the Specification

The Examiner objected to the presence of references to hyperlinks and/or other forms of browser-executable code in the specification (Office Action, page 4). Applicants did not intend to have active links in the specification, nor to incorporate the subject matter of websites by reference to such hyperlinks. Applicants have amended the specification to remove active hyperlinks and therefore respectfully request that the Examiner withdraw the objection to the specification.

Applicants have also amended Tables 1-4 to make the SEQ ID NO correspond to those of the sequence listing. For example, the Incyte ID 1459372CD1 clearly corresponds to SEQ ID NO:11 as shown on page 9 of the Sequence Listing. The Incyte ID 1459372CB1 clearly corresponds to SEQ ID NO:22 as shown on page 15 of the Sequence Listing. The corrections to the SEQ ID NOs in the tables are necessary in order to make them correctly correspond to the Sequence listing, and Applicants respectfully request that the Examiner enter this amendment. Withdrawal of the objection to the specification is respectfully requested.

Utility Rejections under 35 U.S.C. §101 and §112, First Paragraph

Claims 1-3, 5-7, 9, 11, 13, 15-17, and 31 have been rejected under 35 U.S.C. §101 and §112, first paragraph, because the claimed invention allegedly "is not supported by either a specific and substantial asserted utility or a well-established utility" (Office Action, page 4). These rejections are traversed.

The rejection of claims 1-3, 5-7, 9, 11, 13, 15-17, and 31 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification,

and/or a utility well known to one of ordinary skill in the art.

The invention at issue comprises polynucleotides expressed in cardiovascular, reproductive, and hematopoietic/immune system tissues (Specification, e.g., at Table 3). The invention also comprises polypeptides encoded by the claimed polynucleotides. The claimed polypeptides are identified in the patent application as human chaperone proteins, abbreviated as HCPN. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide actually functions.

The fact that the claimed polypeptide is a member of the HSP40/DnaJ chaperone family alone demonstrates utility. Each of the members of this class, regardless of their particular functions, are useful. There is no evidence that any member of this class of polypeptides, let alone a substantial number of them, would not have some patentable utility. It follows that there is a more than substantial likelihood that the claimed polypeptide also has patentable utility, regardless of its actual function. The law has never required a patentee to prove more.

There is, in addition, direct proof of the utility of the claimed invention.

Applicants further submit with this Response three expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and 10 scientific references. The Rockett Declaration, Bedilion Declaration, Iyer Declaration, and the 10 references fully establish that, prior to the October 22, 1999 filing date of the Tang '924 application, it was well-established in the art that:

> expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts; in toxicology, particularly toxicology studies conducted early in drug development efforts; and in phenotypic characterization and categorization of cell types, including neoplastic cell types;
>
> expression analysis can be performed by measuring expression of either proteins or of their encoding transcripts;
>
> it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;
>
> antibodies can routinely be prepared that specifically identify the protein immunogen; used as gene expression probes, such antibodies generate a signal that is specific to the protein, that is, produce a gene-specific expression signal;

each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;

biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

failure of a probe to detect changes in expression of its cognate gene (because such changes did not occur in a particular experiment) does not diminish the usefulness of the probe as a research tool, because such information is itself useful; and

failure of a probe completely to detect its cognate transcript in any particular expression analysis experiment (because the protein is not normally expressed in that sample) does not deprive the probe of usefulness to the community of users who would use it as a research tool.

Applicants file herewith:

1. the Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with Exhibits A-Q (hereinafter the "Rockett Declaration");
2. the Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132 (hereinafter the "Bedilion Declaration");
3. the Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E (hereinafter the "Iyer Declaration"); and
4. 10 references published before the October 22, 1999 filing date of the Tang '924 application:
   a) PCT application WO 95/21944, SmithKline Beecham Corporation, Differentially expressed genes in healthy and diseased subjects (August 17, 1995) (Reference No. 1)
   b) PCT application WO 95/20681, Incyte Pharmaceuticals, Inc., Comparative gene transcript analysis (August 3, 1995) (Reference No. 2)
   c) M. Schena et al., Quantitative monitoring of gene expression patterns with a complementary DNA microarray, Science 270:467-470 (October 20, 1995) (Reference No. 3)

d) PCT application WO 95/35505, Stanford University, Method and apparatus for fabricating microarrays of biological samples (December 28, 1995) (Reference No. 4)

e) U.S. Pat. No. 5,569,588, M. Ashby et al., Methods for drug screening (October 29, 1996) (Reference No. 5)

f) R. A. Heller al., Discovery and analysis of inflammatory disease-related genes using cDNA microarrays, Proc. Natl. Acad. Sci. USA 94:2150 - 2155 (March 1997) (Reference No. 6)

g) PCT application WO 97/13877, Lynx Therapeutics, Inc., Measurement of gene expression profiles in toxicity determinations (April 17, 1997) (Reference No. 7)

h) Acacia Biosciences Press Release (August 11, 1997) (Reference No. 8)

i) V. Glaser, Strategies for Target Validation Streamline Evaluation of Leads, Genetic Engineering News (September 15, 1997) (Reference No. 9)

j) J. L. DeRisi et al., Exploring the metabolic and genetic control of gene expression on a genomic scale, Science 278:680 - 686 (October 24, 1997) (Reference No. 10)

The Patent Examiner contends that the claimed polypeptide cannot be useful without precise knowledge of its biological function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Rockett Declaration, the Bedilion Declaration, and the Iyer Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene and protein expression monitoring applications including toxicology testing are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public.

Brenner v. Manson, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examining Procedure at § 706.03(a).

Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Uses of the claimed polypeptides and polynucleotides for diagnosis of conditions and disorders characterized by expression of HCPN, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Rockett Declaration, Bedilion Declaration, and Iyer Declaration accompanying this Response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The claimed polypeptide's membership in the HSP40/DnaJ chaperone family demonstrates utility

Because there is a substantial likelihood that the claimed HCPN is a member of the HSP40/DnaJ family of chaperones, the members of which are indisputably useful, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Applicants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed that the claimed polypeptide is a protein having the sequence shown as SEQ ID NO:11 in the patent application and referred to as HCPN in that application. Applicants have demonstrated by more than reasonable probability that HCPN is a member of the HSP40/DnaJ family of chaperones, and that the HSP40/DnaJ family of chaperones play roles in protein folding of newly synthesized proteins (see specification, for example, at page 2 and at Table 2). Members of the HSP40/DnaJ family prevent the aggregation and misfolding of proteins, prevent non productive interactions with other cell components, direct assembly of multiprotein complexes, and regulate HSP70 chaperones (see enclosed article of Fink (1999) Physiol. Rev. 79:425-449).

The Examiner must accept the applicant's demonstration that the claimed polypeptide is a member of HSP40/DnaJ chaperone family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Examiner provided any evidence that any member of the HSP40/DnaJ chaperone family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the claimed polypeptide must be, like the other members of the HSP40/DnaJ chaperone family, useful.

B. The uses of HCPN for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene and protein expression profiling. These uses are explained in detail in the accompanying Rockett Declaration, Bedilion Declaration, and Iyer Declaration. The claimed invention is in fact a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity.

This United States patent application, U.S. Ser. No. 10/049,742, filed January 28, 2002 (hereinafter the Yue '742 application), is the National Stage of International Application No.

PCT/US00/21313, filed August 3, 2000, which claims the benefit under 35 U.S.C. § 119(e) of provisional application U.S. Ser. No. 60/160,924, filed October 22, 1999 (hereinafter the Tang '924 application), among others. The Tang '924 application contains the same disclosure with respect to the claimed invention as the Yue '742 application. For the sake of convenience, Applicants cite to and discuss the Yue '742 specification below on the understanding that the descriptions in that specification have the October 22, 1999 priority date of the Tang '924 application.

In his Declaration, Dr. Rockett explains the many reasons why a person skilled in the art in 1999 would have understood that any expressed polypeptide or expressed polynucleotide is useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies or cDNA microarrays, in connection with the development of drugs and the monitoring of the activity of such drugs. (Rockett Declaration at, e.g., ¶¶ 10-18).

> It is widely understood among molecular and cellular biologists that protein expression levels provide complementary profiles for any given cell and cellular state. [Rockett Declaration, ¶ 11.]
>
> Thus, as with nucleic acid microarrays, the greater the number of proteins detectable, the greater the power of the technique; the absence or failure of a protein to change in expression levels does not diminish the usefulness of the method; and prior knowledge of the biological function of the protein is not required. As applied to protein expression profiling, these principles have been well understood since at least as early as the 1980s. [Rockett Declaration, ¶ 14.]
>
> It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s -- and as regards protein profiling, even earlier -- that disclosure of the sequence of a new . . . protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the . . . protein in expression profiling studies in toxicology.[1] [Rockett Declaration, ¶ 18.]

In his Declaration, Dr. Bedilion explains why a person of skill in the art in 1999 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays. (Bedilion Declaration, e.g., ¶¶ 4-7.) In his Declaration,

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"Use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

Dr. Iyer explains why a person of skill in the art in 1999 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that "[t]o provide maximum versatility as a research tool, the microarray should include – and as a biologist I would want my microarray to include – each newly identified gene as a probe." (Iyer Declaration, ¶ 9.)

C. The use of the claimed polypeptide in gene and protein expression monitoring applications using 2-D PAGE gels is disclosed in the Specification and is well known in the art

As described in the Specification and as well known in the art at the time of filing, the claimed polypeptide can be used in gene and protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate.

2-D PAGE technologies were developed during the 1980s. Since the early 1990s, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, e.g., in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed.

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it.

1. Disclosure of gene and protein expression monitoring assays in the Specification

The Yue '742 application discloses that the polynucleotide sequences disclosed therein, including the polynucleotides encoding the SEQ ID NO:11 polypeptide, are useful as probes in chip based technologies. It further teaches that the chip based technologies can be used "for the detection and/or quantification of nucleic acid or protein" (Yue '742 application at page 31).

The Yue '742 application also discloses that the SEQ ID NO:11 polypeptide is useful in protein expression detection technologies. The Yue '742 application states that "[i]mmunological methods for detecting and measuring the expression of HCPN using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS)." (Yue '742 application at page 31, line 32 through page 32, line 1). Furthermore, the Yue '742 application discloses that "[a] variety of protocols for measuring HCPN, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of HCPN expression. Normal or standard values for HCPN expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, for example, human subjects, with antibody to HCPN under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of HCPN expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease." (Yue '742 application at page 48, lines 14-21).

Furthermore, the Tang '924 disclosure regarding the uses of the SEQ ID NO:11 polypeptide for protein expression monitoring applications is <u>not</u> limited to the use of that protein in 2-D PAGE maps. For one thing, the Yue '742 disclosure regarding the technique used in gene and protein expression monitoring applications is broad (Yue '742 application at, e.g., page 31, lines 27-31).

In addition, the Yue '742 specification repeatedly teaches that the protein described therein (including the SEQ ID NO:11 polypeptide) may desirably be used in any of a number of long established "standard" techniques, such as ELISA or western blot analysis, for conducting protein expression monitoring studies. See, e.g.:

(a) Yue '742 application at page 31, line 32 through page 32, line 1 ("Immunological methods for detecting and measuring the expression of HCPN using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS)");

(b) Yue '742 application at page 48, lines 14-21 ("A variety of protocols for measuring HCPN, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of HCPN expression. Normal or standard values for HCPN expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, for example, human subjects, with antibody to HCPN under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of HCPN expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease").

2. Disclosure of gene and protein expression monitoring assays in the art

A number of published articles and patent documents provide evidence that gene and protein expression monitoring techniques were well-known before the October 22, 1999 filing date of the Yue '742 application.

At the time of filing the Yue '742 application, it was well known in the art that gene and protein expression analyses also included two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) technologies, which were developed during the 1980s, as exemplified by the Anderson 1991 and 1995 articles (Reference No. 12 and Reference No. 13). The Anderson 1991 article teaches that a 2-D PAGE map has been used to connect and compare hundreds of 2-D gels of rat liver samples from a variety of studies including regulation of protein expression by various drugs and toxic agents (Reference No. 12 at page 907). The Anderson 1991 article teaches an empirically-determined standard curve fitted to a series of identified proteins based upon amino acid chain length (Reference No. 12 at page 911) and how that standard curve can be used in protein expression analysis. The Anderson 1991 article teaches that "there is a long-term need for a comprehensive database of liver proteins" (Reference No. 12 at page 912).

Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, Reference No. 13, page 26.)

The toxicity (or lack of toxicity) of any proposed drug is one of the most important criteria to be considered and evaluated in connection with the development of the drug. Good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identification of undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of the development of any new drug. In fact, the desire to identify and understand toxicological effects using the experimental assays described above led Dr. Leigh Anderson to found the Large Scale Biology Corporation in 1985, in order to pursue commercial development of the 2-D electrophoretic protein mapping technology he had developed. In addition, the company focused on toxicological effects on the proteome as clearly demonstrated by its goals and by its senior management credentials described in company documents (see Reference No. 18 at pages 1, 3, and 5).

The Celis article stated that "protein databases are expected to foster a variety of biological information.... -- among others, ... drug development and testing" (See Reference No. 15, page 2200, second column). The Franzen article shows that 2-D PAGE maps were used to identify proteins in clinical tumor material (See Reference No. 16). The Yue '742 application clearly discloses that expression of HCPN is associated with cardiovascular, reproductive, and hematopoietic/immune system tissues (Yue '742 Specification, e.g., at Table 3). The Bjellqvist article showed that a protein may be identified accurately by its positional coordinates, namely molecular mass and isoelectric point (See Reference No. 17). The Yue '742 application clearly disclosed SEQ ID NO:11 from which it would have been routine for one of skill in the art to

predict both the molecular mass and the isoelectric point using algorithms well known in the art at the time of filing.

Expressed proteins are useful for 2-D PAGE analysis in toxicology expression studies for a variety of reasons, particularly for purposes relating to providing controls for the 2-D PAGE analysis, and for identifying sequence or post-translational variants of the expressed polypeptides in response to exogenous compounds.

3. Conclusion

Thus a person skilled in the art on October 22, 1999, who read the Tang '924 specification, would have routinely and readily appreciated that the SEQ ID NO:11 polypeptide disclosed therein would be useful for conducting gene and protein expression monitoring analyses using 2-D PAGE mapping or western blot analysis or any of the other traditional membrane-based protein expression monitoring techniques that were known and in common use many years prior to the filing of the Tang '924 application. For example, a person skilled in the art on October 22, 1999 would have routinely and readily appreciated that the SEQ ID NO:11 polypeptide would be a useful tool in conducting protein expression analyses, using the 2-D PAGE mapping or western analysis techniques, for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity.

D. The use of polypeptides expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, e.g., as described by Rockett and Iyer in their Declarations.

Toxicology testing is now standard practice in the pharmaceutical industry. See, e.g., John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (Rockett Declaration, Exhibit C):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Rockett Declaration, Exhibit C, page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Reference No. 19); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No. 20).

The more genes – and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator of the Nuwaysir paper, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 21) Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

Further evidence of the well-established utility of all expressed polypeptides and polynucleotides in toxicology testing is found in U.S. Pat. No. 5,569,588 (Reference No. 5) and published PCT applications WO 95/21944 (Reference No. 1), WO 95/20681 (Reference No. 2), and WO 97/13877 (Reference No. 7), the Acacia Biosciences Press Release (Reference No. 8), and the Glaser article (Reference No. 9).

U.S. Pat. No. 5,569,588 ("Methods for Drug Screening") ("the '588 patent"), issued October 29, 1996, with a priority date of August 9, 1995, describes an expression profiling platform, the "genome reporter matrix," which is based upon the measurement of protein expression levels. The '588 patent further describes use of nucleic acid microarrays to measure transcript expression levels, making clear that the utility of comparing multidimensional expression data sets equally applies to protein expression data and transcript expression data.

The '588 patent speaks clearly to the usefulness of such expression analyses, particularly but not exclusively protein expression profiling, in drug development and toxicology, particularly

pointing out that a protein's failure to change in expression level is a useful result. Thus, with emphasis added,

> [The invention provides] methods and compositions for modeling the transcriptional responsiveness of an organism to a candidate drug. . . . [The final step of the method comprises] comparing reporter gene product signals for each cell before and after contacting the cell with the candidate drug to <u>obtain a drug response profile</u> which provides a model of the transcriptional responsiveness of said organism to the candidate drug. [abstract]
>
> The present invention exploits the recent advances in genome science to provide for the rapid screening of large numbers of compounds against a systemic target comprising <u>substantially all targets in a pathway [or] organism</u>. [column 1]
>
> The ensemble of reporting cells comprises as comprehensive a collection of transcription regulatory genetic elements as is conveniently available for the targeted organism so as to most accurately model the systemic transcriptional response. <u>Suitable ensembles generally comprise thousands of individually reporting elements; preferred ensembles are substantially comprehensive, i.e. provide a transcriptional response diversity comparable to that of the target organism. Generally, a substantially comprehensive ensemble requires transcription regulatory genetic elements from at least a majority of the organism's genes, and preferably includes those of all or nearly all of the genes</u>. We term such a substantially comprehensive ensemble a genome reporter matrix. [column 2]
>
> Drugs often have side effects that are in part due to the lack of target specificity. . . . [A] genome reporter matrix reveals the spectrum of other genes in the genome also affected by the compound. In considering two different compounds both of which induce the ERG10 reporter, if one compound affects the expression of 5 other reporters and a second compound affects the expression of 50 other reports, the first compound is, a priori, more likely to have fewer side effects. [columns 2-3]
>
> Furthermore, <u>it is not necessary to know the identity of any of the responding genes</u>. [column 3]
>
> [A]ny new compound that induces the same response profile as [a] . . . dominant tubulin mutant would provide a candidate for a taxol-like pharmaceutical. [column 4]
>
> The genome reporter matrix offers a simple solution to recognizing new specificities in combinatorial libraries. Specifically, pools of new compounds are tested as mixtures across the matrix. If the pool has any new activity not present

in the original lead compound, new genes are affected among the reporters. [column 4]

A sufficient number of different recombinant cells are included to provide an ensemble of transcriptional regulatory elements of said organism sufficient to model the transcriptional responsiveness of said organism to a drug. In a preferred embodiment, the matrix is substantially comprehensive for the selected regulatory elements, e.g. essentially all of the gene promoters of the targeted organism are included. [columns 6-7]

In a preferred embodiment, the basal response profiles are determined. . . . The resultant electrical output signals are stored in a computer memory as genome reporter output signal matrix data structure associating each output signal with the coordinates of the corresponding microtiter plate well and the stimulus or drug. This information is indexed against the matrix to form <u>reference response profiles</u> that are used to determine the response of each reporter to any milieu in which a stimulus may be provided. After establishing a basal response profile for the matrix, each cell is contacted with a candidate drug. The term drug is used loosely to refer to agents which can provoke a specific cellular response. . . . <u>The drug induces a complex response pattern</u> of repression, silence and induction across the matrix . . . .The response profile reflects the cell's transcriptional adjustments to maintain homeostasis in the presence of the drug. . . . After contacting the cells with the candidate drug, the reporter gene product signals from each of said cells is again measured to determine a stimulated response profile. The basal o[r] background response profile is then compared with . . . the stimulated response profile to identify the cellular response profile to the candidate drug. [columns 7-8]

<u>In another embodiment of the invention</u>, <u>a matrix [i.e., array] of hybridization probes corresponding to a predetermined population of genes of the selected organism is used</u> to specifically detect changes in gene transcription which result from exposing the selected organism or cells thereof to a candidate drug. In this embodiment, one or more cells derived from the organism is exposed to the candidate drug in vivo or ex vivo under conditions wherein the drug effects a change in gene transcription in the cell to maintain homeostasis. Thereafter, the gene transcripts, primarily mRNA, of the cell or cells is isolated . . . [and] then contacted with an ordered matrix [array] of hybridization probes, each probe being specific for a different one of the transcripts, <u>under conditions where each of the transcripts hybridizes with a corresponding one</u> of the probes to form hybridization pairs. The ordered matrix of probes provides, in aggregate, complements for an ensemble of genes of the organism sufficient to model the transcriptional responsiveness of the organism to a drug. . . . The <u>matrix-wide signal profile of the drug-stimulated cells is then compared with a matrix-wide signal profile of negative control cells to obtain a specific drug response profile</u>. [column 8]

> The invention also provides means for computer-based qualitative analysis of candidate drugs and unknown compounds. A wide variety of reference response profiles may be generated and used in such analyses. [column 8]
>
> Response profiles for an unknown stimulus (e.g. new chemicals, unknown compounds or unknown mixtures) may be analyzed by comparing the new stimulus response profiles with response profiles to known chemical stimuli. [column 9]
>
> The response profile of a new chemical stimulus may also be compared to a known genetic response profile for target gene(s). [column 9]

The August 11, 1997 press release from the '588 patent's assignee, Acacia Biosciences (now part of Merck) (Reference No. 8), and the September 15, 1997 news report by Glaser, Strategies for Target Validation Streamline Evaluation of Leads, Genetic Engineering News (Reference No. 9), attest the commercial value of the methods and technology described and claimed in the '588 patent.

WO 95/21944 ("Differentially expressed genes in healthy and diseased subjects"), published August 17, 1995, describes the use of nucleic acid microarrays in expression profiling analyses, emphasizing that *patterns* of expression can be used to distinguish healthy tissues from diseased tissues and that *patterns* of expression can additionally be used in drug development and toxicology studies, without knowledge of the biological function of the encoded gene product. In particular, and with emphasis added:

> The present invention involves . . . methods for diagnosing diseases . . . characterized by the presence of [differentially expressed] . . . genes, despite the absence of knowledge about the gene or its function. The methods involve the use of a composition suitable for use in hybridization which consists of a solid surface on which is immobilized at pre-defined regions thereon a plurality of defined oligonucleotide/ polynucleotide sequences for hybridization. Each sequence comprises a fragment of an EST. . . . Differences in hybridization patterns produced through use of this composition and the specified methods enable diagnosis of diseases based on differential expression of genes of unknown function . . . . [abstract]
>
> The method [of the present invention] involves producing and comparing hybridization patterns formed between samples of expressed mRNA or cDNA polynucleotide sequences . . . and a defined set of oligonucleotide/polynucleotide[] . . . immobilized on a support. Those defined [immobilized] oligonucleotide/polynucleotide sequences are representative of the total expressed

genetic component of the cells, tissues, organs or organism as defined by the collection of partial cDNA sequences (ESTs). [page 2]

The present invention meets the unfilled needs in the art by providing methods for the . . . use of gene fragments and genes, even those of unknown full length sequence and unknown function, which are differentially expressed in a healthy animal and in an animal having a specific disease or infection by use of ESTs derived from DNA libraries of healthy and/or diseased/infected animals. [page 4]

Yet another aspect of the invention is that it provides . . . a means for . . . monitoring the efficacy of disease treatment regimes including . . . toxicological effects thereof. [page 4]

It has been appreciated that one or more differentially identified EST or gene-specific oligonucleotide/polynucleotides define a pattern of differentially expressed genes diagnostic of a predisease, disease or infective state. A knowledge of the specific biological function of the EST is not required only that the EST[] identifies a gene or genes whose altered expression is associated reproducibly with the predisease, disease or infectious state. [page 4]

As used herein, the term 'disease' or 'disease state' refers to any condition which deviates from a normal or standardized healthy state in an organism of the same species in terms of differential expression of the organism's genes. . . [whether] of genetic or environmental origin, for example, an inherited disorder such as certain breast cancers. . . .[or] administration of a drug or exposure of the animal to another agent, e.g., nutrition, which affects gene expression. [page 5]

As used herein, the term 'solid support' refers to any known substrate which is useful for the immobilization of large numbers of oligonucleotide/polynucleotide sequences by any available method . . . [and includes, inter alia,] nitrocellulose, . . . glass, silica. . . . [page 6]

By 'EST' or 'Expressed Sequence Tag' is meant a partial DNA or cDNA sequence of about 150 to 500, more preferably about 300, sequential nucleotides. . . . [page 6]

One or more libraries made from a single tissue type typically provide at least about 3000 different (i.e., unique) ESTs and potentially the full complement of all possible ESTs representing all cDNAs e.g., 50,000 – 100,000 in an animal such as a human. [page 7]

The lengths of the defined oligonucleotide/ polynucleotides may be readily increased or decreased as desired or needed. . . . The length is generally guided by the principle that it should be of sufficient length to insure that it is on[] average only represented once in the population to be examined. [page 7]

> Comparing the . . . hybridization patterns permits detection of those defined oligonucleotide/ polynucleotides which are differentially expressed between the healthy control and the disease sample by the presence of differences in the hybridization patterns at pre-defined regions [of the solid support]. [page 13]
>
> It should be appreciated that one does not have to be restricted in using ESTs from a particular tissue from which probe RNA or cDNA is obtained[;] rather any or all ESTs (known or unknown) may be placed on the support. Hybridization will be used [to] form diagnostic patterns or to identify which particular EST is detected. For example, all known ESTs from an organism are used to produce a 'master' solid support to which control sample and disease samples are alternately hybridized. [page 14]
>
> Diagnosis is accomplished by comparing the two hybridization patterns, wherein substantial differences between the first and second hybridization patterns indicate the presence of the selected disease or infection in the animal being tested. Substantially similar first and second hybridization patterns indicate the absence of disease or infection. This[,] like many of the foregoing embodiments[,] may use known or unknown ESTs derived from many libraries. [page 18]
>
> Still another intriguing use of this method is in the area of monitoring the effects of drugs on gene expression, both in laboratories and during clinical trials with animal[s], especially humans. [page 18]

WO 95/20681 ("Comparative Gene Transcript Analysis"), filed in 1994 by Applicants' assignee and published August 3, 1995, has three issued U.S. counterparts: U.S. Pat. Nos. 5,840,484, issued November 24, 1998; 6,114,114, issued September 5, 2000; and 6,303,297, issued October 16, 2001.

The specification describes the use of transcript expression *patterns,* or "images", each comprising multiple pixels of gene-specific information, for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts. The specification describes a plurality of methods for obtaining the requisite expression data -- one of which is microarray hybridization -- and equates the uses of the expression data from these disparate platforms. In particular, and with emphasis added:

> [The invention provides a] method and system for quantifying the relative abundance of gene transcripts in a biological specimen. . . . [G]ene transcript imaging can be used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. The invention provides a method for comparing the gene transcript image analysis from two or more different biological specimens

in order to distinguish between the two specimens and identify one or more genes which are differentially expressed between the two specimens. [abstract]

[W]e see each individual gene product as a 'pixel' of information, which relates to the expression of that, and only that, gene. We teach herein [] methods whereby the individual 'pixels' of gene expression information can be combined into a single gene transcript 'image,' in which each of the individual genes can be visualized simultaneously and allowing relationships between the gene pixels to be easily visualized and understood. [page 2]

The present invention avoids the drawbacks of the prior art by providing a method to quantify the relative abundance of multiple gene transcripts in a given biological specimen. . . . The method of the instant invention provides for detailed diagnostic comparisons of cell profiles revealing numerous changes in the expression of individual transcripts. [page 6]

High resolution analysis of gene expression be used directly as a diagnostic profile. . . . [page 7]

The method is particularly powerful when more than 100 and preferably more than 1,000 gene transcripts are analyzed. [page 7]

The invention . . . includes a method of comparing specimens containing gene transcripts. [page 7]

The final data values from the first specimen and the further identified sequence values from the second specimen are processed to generate ratios of transcript sequences, which indicate the differences in the number of gene transcripts between the two specimens. [i.e., the results yield analogous data to microarrays] [page 8]

Also disclosed is a method of producing a gene transcript image analysis by first obtaining a mixture of mRNA, from which cDNA copies are made. [page 8]

In a further embodiment, the relative abundance of the gene transcripts in one cell type or tissue is compared with the relative abundance of gene transcript numbers in a second cell type or tissue in order to identify the differences and similarities. [page 9]

In essence, the invention is a method and system for quantifying the relative abundance of gene transcripts in a biological specimen. The invention provides a method for comparing the gene transcript image from two or more different biological specimens in order to distinguish between the two specimens. . . . [page 9]

[T]wo or more gene transcript images can be compared and used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. [pages 9-10]

The present invention provides a method to compare the relative abundance of gene transcripts in different biological specimens. . . . This process is denoted herein as gene transcript imaging. The quantitative analysis of the relative abundance for a set of gene transcripts is denoted herein as "gene transcript image analysis" or "gene transcript frequency analysis". The present invention allows one to obtain a profile for gene transcription in any given population of cells or tissue from any type of organism. [page 11]

The invention has significant advantages in the fields of diagnostics, toxicology and pharmacology, to name a few. [page 12]

[G]ene transcript sequence abundances are compared against reference database sequence abundances including normal data sets for diseased and healthy patients. The patient has the disease(s) with which the patient's data set most closely correlates. [page 12]

For example, gene transcript frequency analysis can be used to differentiate normal cells or tissues from diseased cells or tissues. . . . [page 12]

In toxicology, . . . [g]ene transcript imaging provides highly detailed information on the cell and tissue environment, some of which would not be obvious in conventional, less detailed screening methods. The gene transcript image is a more powerful method to predict drug toxicity and efficacy. Similar benefits accrue in the use of this tool in pharmacology. . . . [page 12]

In an alternative embodiment, comparative gene transcript frequency analysis is used to differentiate between cancer cells which respond to anti-cancer agents and those which do not respond. [page 12]

In a further embodiment, comparative gene transcript frequency analysis is used . . . for the selection of better pharmacologic animal models. [page 14]

In a further embodiment, comparative gene transcript frequency analysis is used in a clinical setting to give a highly detailed gene transcript profile of a diseased state or condition. [page 14]

An alternate method of producing a gene transcript image includes the steps of obtaining a mixture of test mRNA and providing a representative array of unique probes whose sequences are complementary to at least some of the test mRNAs. Next, a fixed amount of the test mRNA is added to the arrayed probes. The test

> mRNA is incubated with the probes for a sufficient time to allow hybrids of the test mRNA and probes to form. The mRNA-probe hybrids are detected and the quantity determined. [page 15]
>
> [T]his research tool provides a way to get new drugs to the public faster and more economically. [page 36]
>
> In this method, the particular physiologic function of the protein transcript need not be determined to qualify the gene transcript as a clinical marker. [page 38]
>
> [T]he gene transcript changes noted in the earlier rat toxicity study are carefully evaluated as clinical markers in the followed patients. Changes in the gene transcript image analyses are evaluated as indicators of toxicity by correlation with clinical signs and symptoms and other laboratory results. . . . The . . . analysis highlights any toxicological changes in the treated patients. [page 39]

WO 97/13877 ("Measurement of Gene Expression Profiles in Toxicity Determinations"), filed on October 11, 1996 and published on April 17, 1997 (shortly after the April 8, 1997 filing date of the parent application for the instant U.S. Serial No. 09/203,545 application), describes an expression profiling technology differing somewhat from the use of cDNA microarrays and differing from the genome reporter matrix of the '588 patent; but the use of the data is analogous. As per its title, the WO 97/13877 publication describes use of expression profiling in toxicity determinations. In particular, and with emphasis added:

> [T]he invention relates to a method for detecting and monitoring changes in gene expression patterns in in vitro and in vivo systems for determining the toxicity of drug candidates. [Field of the invention]
>
> An object of the invention is to provide a new approach to toxicity assessment based on an examination of gene expression patterns, or profiles, in in vitro or in vivo test systems. [page 3]
>
> Another object of the invention is to provide a rapid and reliable method for correlating gene expression with short term and long term toxicity in test animals. [page 3]
>
> The invention achieves these and other objects by providing a method for massively parallel signature sequencing of genes expressed in one or more selected tissues of an organism exposed to a test compound. An important feature of the invention is the application of novel . . . methodologies that permit the formation of gene expression profiles for selected tissues . . . . Such profiles may be compared with those from tissues of control organisms at single or multiple time points to identify expression patterns predictive of toxicity. [page 3]

> As used herein, the terms "gene expression profile," and "gene expression pattern" which is used equivalently, means a frequency distribution of sequences of portions of cDNA molecules sampled from a population of tag-cDNA conjugates. . .. Preferably, the total number of sequences determined is at least 1000; more preferably, the total number of sequences determined in a gene expression profile is at least ten thousand. [page 7]
>
> The invention provides a method for determining the toxicity of a compound by analyzing changes in the gene expression profiles in selected tissues of test organisms exposed to the compound. . . . . Gene expression profiles derived from test organisms are compared to gene expression profiles derived from control organisms. . . . [page 7]

In fact, the potential benefit to the public of having the claimed expressed polypeptide, in terms of lives saved and reduced health care costs, are enormous. Evidence of the benefits of this information include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

E. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing the sequences of all expressed genes (along with the polypeptide translations of those genes). (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the sequence of the claimed polypeptide and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. For example, Page et al., in discussing the identification and assignment of candidate targets, states that "rapid identification and assignment of candidate targets and markers represents a huge challenge . . . [t]he process of annotation is similarly aided by the quality and richness of the sequence specific databases that are currently available, both in the public domain and in the private sector (e.g. those supplied by Incyte Pharmaceuticals)" (Page, M.J., Amess, B., Rohlff, C., Stubberfield, C., Parekh, R., <u>Proteomics: a major new technology for the drug discovery process</u>, Drug Discov. Today 4:55-62 (1999), Reference No. 22, enclosed, see page 58, col. 2). As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polypeptide, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

Customers can, moreover, purchase polynucleotides encoding the claimed polypeptide directly from Incyte, saving the customer the time and expense of isolating and purifying or cloning the polynucleotide for research uses such as those described *supra*.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polypeptide are not specific and substantial or well-established utilities. (Office Action at page 5.) The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role Or Function Of An Expressed Polypeptide Is Not Required To Demonstrate Utility

One of the Examiner's grounds of rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Rockett Declaration (at, *e.g.*, ¶¶ 10-18), the Bedilion Declaration (at, *e.g.*, ¶¶ 4-7), and the Iyer Declaration (at, *e.g.*, ¶¶ 5-10), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed polypeptide, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the claimed polypeptide is a member of HSP40/DnaJ chaperone family, whose members indisputably are useful, the Examiner refused to impute the utility of the members of the HSP40/DnaJ chaperone family to HCPN. In the Office Action, the Patent Examiner takes the position that unless Applicants can identify which particular biological function within the class of HSP40/DnaJ chaperone is possessed by HCPN, utility cannot be imputed. To demonstrate utility by membership in the class of HSP40/DnaJ chaperone, the Examiner would require that all HSP40/DnaJ chaperone possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the

members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a substantial number of useless members. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).[2]

The Examiner addresses HCPN as if the general class in which it is included is not the HSP40/DnaJ chaperone family, but rather all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the HSP40/DnaJ chaperone family does not. The HSP40/DnaJ chaperone family is sufficiently specific to rule out any reasonable possibility that HCPN would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the HSP40/DnaJ chaperone class of proteins has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the HCPN encoded by the claimed polypeptide is useful.

Even if the Examiner's "common utility" criterion were correct – and it is not – the HSP40/DnaJ chaperone family would meet it. It is undisputed that known members of the HSP40/DnaJ chaperone family function in protein folding. A person of ordinary skill in the art need not know any more about how the claimed invention functions to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation that a person of ordinary skill in the art would need to confirm the function or activity of any given member of the HSP40/DnaJ chaperone family. The Examiner then goes on to assume that

[2]At a Biotechnology Customer Partnership Meeting, PTO Senior Examiner James Martinell described an analytical framework roughly consistent with this analysis. He stated that when an applicant's claimed protein "is a member of a family of proteins that already are known based upon sequence homology," that can be an effective assertion of utility.

the only use for HCPN absent knowledge as to how this member of the HSP40/DnaJ chaperone family actually works is further study of HCPN itself.

C. The uses of HCPN in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

The Examiner rejected the claims at issue on the ground that the use of an invention as tool for research is not a "substantial" use. Because the Examiner's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (Section 2107.01 of the Manual of Patent Examining Procedure, 8th Edition, February 2003 revision, under the heading I. Specific and Substantial Requirements, Research Tools):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

The PTO's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by the PTO's Training Materials to be useful.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that

would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

Such beneficial uses beyond studying the claimed invention itself have been demonstrated, in particular those described in the Rockett Declaration, the Bedilion Declaration, and the Iyer Declaration. The Rockett Declaration, the Bedilion Declaration, and the Iyer Declaration demonstrate that the claimed invention is a tool, rather than an object, of research, and it demonstrates exactly how that tool is used. Without the claimed invention, it would be more difficult to generate information regarding the properties of tissues, cells, drug candidates and toxins apart from additional information about the polypeptide itself.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene and protein expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polypeptide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete (e.g., Rockett Declaration at ¶¶ 10-18 and Iyer Declaration at ¶¶ 3-9).

The use of the claimed invention as a research tool in toxicology testing is specific and substantial. While it is true that all polypeptides and polynucleotides expressed in humans have utility in toxicology testing based on the property of being expressed at some time in development or in the cell life cycle, this basis for utility does not preclude that utility from being specific and substantial. A toxicology test using any particular expressed polypeptide or polynucleotide is dependent on the **identity** of that polypeptide or polynucleotide, not on its biological function or its disease association. The results obtained from using any particular human-expressed polypeptide or polynucleotide in toxicology testing is specific to both the compound being tested and the polypeptide polynucleotide used in the test. **No two human-expressed polypeptides or polynucleotides are interchangeable for toxicology testing** because the effects on the expression of any two such polypeptides or polynucleotides will differ depending on the identity

of the compound tested and the **identities** of the two polypeptides or polynucleotides. It is not necessary to know the biological functions and disease associations of the polypeptides or polynucleotides in order to carry out such toxicology tests. Therefore, at the very least, the claimed polypeptides or polynucleotides are specific controls for toxicology tests in developing drugs targeted to other polypeptides or polynucleotides, and are clearly useful as such.

As an example, any histone gene or protein expressed in humans can be used in a specific and substantial toxicology test in drug development. A histone gene or protein may not be suitable as a target for drug development because disruption of such a gene may kill a patient. However, a human-expressed histone gene or protein is surely an excellent subject for toxicology studies when developing drugs **targeted to other genes or proteins**. A drug candidate which alters expression of a histone gene or protein is toxic because disruption of such a pervasively-expressed gene or protein would have undesirable side effects in a patient. Therefore, when testing the toxicology of a drug candidate targeted to another gene or protein, measuring the expression of a histone gene or protein is a good measure of the toxicity of that candidate, particularly in *in vitro* cellular assays at an early stage of drug development. The utility of any particular human-expressed histone gene or protein in toxicology testing is specific and substantial because a toxicology test using that histone gene or protein cannot be replaced by a toxicology test using a different gene, including any other histone gene or protein. This specific and substantial utility requires no knowledge of the biological function or disease association of the histone gene or protein .

The expression of SEQ ID NO:11 in human tissues would lead a skilled artisan to believe that this polypeptide has some physiological implications, even if these implications have not been precisely identified. During toxicology testing, a change in expression of a human-expressed polypeptide indicates potential toxicity of a drug candidate, even if the physiological implications of that polypeptide are unknown. Such a toxicology test allows one to choose a lead drug candidate which has minimal effects on the expression of proteins other than the protein to which the candidate is targeted. Such a lead drug candidate would be less likely to have unintended side effects than a drug candidate having greater effects on the expression of genes/proteins other than the intended drug target. Thus, the benefit of such a toxicology test is an increased chance of

finding a safe and effective drug, and a corresponding reduction in the expense and time of bringing a drug to market.

The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include uses such as diagnostic assays (e.g., pages 48-56), chromosomal markers (e.g., page 56), ligand screening assays (e.g., pages 33-34), and drug screening (page 56-57).

D. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

The Examiner rejected the pending claims on the ground that the applicant cannot impute utility to the claimed invention based on its homology to another polypeptide undisputed by the Examiner to be useful. The Examiner's rejection is both incorrect as a matter of fact and as a matter of procedural law.

Under the applicable law, once the applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. *See In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not made such a showing and, as such, the Examiner's rejection should be overturned.

1. Applicants' Showing of Facts Overcomes The Examiner's Concern That Applicants' Invention Lacks "Specific Utility"

The Examiner alleges that "the instant invention does not possess a specific or a well-established utility, although there is a general utility that is applicable to the broad class of DnaJ proteins. The utility is not a substantial utility because it requires further research to identify or reasonably confirm a 'real world' context of use." (Office Action, pages 6-7.)

Applicants' submission of the Rockett Declaration (e.g., ¶¶ 11-18) overcomes this concern. The Rockett Declaration demonstrates that, far from applying ***regardless*** of the specific properties of the claimed invention, the utility of Applicants' claimed polypeptide **depends upon** properties -- its amino acid sequence-- that allow it specifically to be identified, for example, by specific antibodies or by 2-D PAGE and mass spectroscopy sequencing of spots on the gel.

Although not required for present purposes, it would be appropriate to state on the record here that the specificity of protein-antibody binding was well-established in the art far earlier than the development of antibody microarrays in the 1980s, and indeed is the well-established underpinning of many, perhaps most, immunoassay techniques over the past several decades.

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § **III.B.** (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously

applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. *See supra* § **III.B.** Thus the Training Materials cannot be applied consistently with the law.

V. To the extent the rejection of the claimed invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under 35 U.S.C. § 112, first paragraph, is based on the improper allegation of lack of patentable utility under 35 U.S.C. § 101, it fails for the same reasons.

CONCLUSION

Applicants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, "like a nose of wax,"[3] to target rejections of claims to polypeptides and polynucleotides where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art.

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[3]"The concept of patentable subject matter under §101 is not 'like a nose of wax which may be turned and twisted in any direction * * *.' *White v. Dunbar*, 119 U.S. 47, 51." *(Parker v. Flook,* 198 USPQ 193 (US SupCt 1978))

As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

Written description rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 3, 6, 7, 9, 11, 13, 15, 16, and 31 have been rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. (footnotes omitted.)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:11 and SEQ ID NO:22 are specifically disclosed in the application (see, for example, page 4, lines 20-24 and 30-32, and page, lines 32-34). Variants of SEQ ID NO:11 and SEQ ID NO:22 are described, for example, at page 24, lines 17-20 and lines 27-35. Incyte clones in which the nucleic acids encoding the human chaperone protein were first identified and libraries from which those clones were isolated are described, for example, at Tables 1 and 4 of the Specification. Chemical and structural features of SEQ ID NO:11 are described, for example, at Table 2. Given SEQ ID NO:11 and SEQ ID NO:22, one of ordinary skill in the art would recognize a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:11, a polynucleotide encoding a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:11, a polynucleotide comprising a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide of SEQ ID NO:22, and fragments of a polypeptide having the sequence of SEQ ID NO:11. Accordingly, the Specification provides an adequate written description of the recited polypeptide sequences.

The Office Action has further asserted that the claims are not supported by an adequate written description because "[t]he lack of a structure to function/activity relationship and the lack of representative species for the polypeptide having at least 90% sequence identity to SEQ ID NO:11, the biologically active fragment of SEQ ID NO:11, the polynucleotide having at least 70% sequence identity to SEQ ID NO:22, or the fragment of SEQ ID NO:22 as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention" (Office Action, page 8).

Such a position is believed to present a misapplication of the law.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court

therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides or polypeptides in terms of chemical structure, rather than functional characteristics. For example, the "variant language" of independent claims 1 and 11 recite chemical structure to define the claimed genus:

> 1. An isolated polypeptide selected from the group consisting of:...
>
> b) a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:11...
>
> 11. An isolated polynucleotide selected from the group consisting of:...
>
> b) a polynucleotide comprising a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide of SEQ ID NO:22...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structures of SEQ ID NO:11 and SEQ ID NO:22. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides or polypeptides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides or polypeptides. The polynucleotides or polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to human chaperone proteins related to the amino acid sequence of SEQ ID NO:11. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as human chaperone proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:11. The "variant language" of the present claims recites, for example, polynucleotides encoding "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:11" (note that SEQ ID NO:11 has 269 amino acid residues). This variation is far less than that of all potential human chaperone proteins related to SEQ ID NO:11, i.e., those human chaperone proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:11.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written

description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of October 22, 1999. Much has happened in the development of recombinant DNA technology in the 22 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:11 and SEQ ID NO:22, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:11 or SEQ ID NO:22. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides or polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 16 and 17 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner alleges that the

term "an effective amount" is indefinite because "it is not clear what the effective amount of polypeptide would do" (Office Action, page 9).

In order to expedite prosecution, the term "an effective amount" has been removed from claim 16; therefore, the rejection on this basis is moot.

For at least the above reasons, withdrawal of the rejection of claim 16 and dependent claim 17 under 35 U.S.C. § 112, second paragraph is respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,
INCYTE CORPORATION

Date: 23 April 2004

James M. Verna, Ph.D.
Reg. No. 33,287
Direct Dial Telephone: (650) 845 -5415

Customer No.: 27904
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

Enclosures:

1. Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, Proc. Nat. Acad. Sci. 94:8945-8947 (1997)
2. Emile F. Nuwaysir et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999);
3. Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000).
4. John C. Rockett and David J. Dix, Application of DNA arrays to toxicology, 107 Environ. Health Perspec. 107:681-685 (1999).

5. Email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding,
6. Brenner et al., Proc. Natl. Acad. Sci. 95:6073-6078 (1998).
7. Page, M.J. et al., Proteomics: a major new technology for the drug discovery process, Drug Discov. Today 4:55-62 (1999).
8. Exhibit A
9. Fink Physiol. Rev. 79:425-449 (1999).

NEW Declarations and References:
1) Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with Exhibits A - Q;
2) Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132;
3) Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A - E; and
4) ten (10) references published before the filing date of the instant application:
a) WO 95/21944, SmithKline Beecham, "Differentially expressed genes in healthy and diseased subjects" (Aug. 17, 1995)
b) WO 95/20681, Incyte Pharmaceuticals, "Comparative Gene Transcript Analysis" (Aug 3, 1995)
c) Schena et al., "Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray," Science 270:467-470 (Oct 20, 1995)
d) WO 95/35505, Stanford University, "Method and apparatus for fabricating microarrays of biological samples" (Dec 28, 1995)
e) U.S. Pat. No. 5,569,588, Ashby et al., "Methods for Drug Screening" (Oct 29, 1996)
f) Heller al., "Discovery and analysis of inflammatory disease-related genes using cDNA microarrays," *PNAS* 94:2150 - 2155 (Mar 1997)
g) WO 97/13877, Lynx Therapeutics, "Measurement of Gene Expression Profiles in Toxicity Determinations" (April 17, 1997)
h) Acacia Biosciences Press Release (August 11, 1997)
i) Glaser, "Strategies for Target Validation Streamline Evaluation of Leads," Genetic Engineering News (Sept. 15, 1997)
j) DeRisi *et al.*, "Exploring the metabolic and genetic control of gene expression on a genomic scale," Science 278:680 - 686 (Oct 24, 1997)